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'Side' effects: A misnomer

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The tragic results for the babies of patients prescribed thalidomide, although they can indeed be termed 'side' effects, hardly warrant so slight an epithet, and Dr Joyce in his paper would like the term to be dropped in favour of 'additional' effects of drugs. Despite extensive clinical trials before drugs are put before the prescribing doctor, side effects cannot be entirely anticipated or eliminated, and indeed many are not harmful. However, it is important, Dr Joyce argues, for information to the doctor from the patient and from the doctor to the manufacturer to be collected and evaluated. Only in this way can effects of drugs other than those intended be drawn to the notice of the manufacturer.

The commentary by two practising physicians emphasizes the ambiguities in the descriptive literature accompanying a new drug. Dr Herxheimer and Dr Higgs would like to see some sort of panel to be established to reassess drugs in the light of observations on their effects and 'side' effects on patients, a task which the existing Committee on Safety of Medicines could not at the moment undertake. A medical need for a new drug should be established before it is manufactured, let alone offered to the general practitioner.

Side effects or additional effects of drugs

The term 'side effects' is seldom if ever satisfactory. Whether an effect arising in addition to the therapeutic result that was sought from the drug is minimal or life threatening, it should never be regarded as something that occurs 'on the side'. A headache, a stuffy nose or a feeling of weariness attract at least momentarily the attention of the patient or he would not report them. Symptoms are therefore not a side issue for the patient, and physical signs should not be so treated by the physician either. Some have been referring for a long time to such events as 'unwanted' effects, but a thoughtful colleague of mine prefers to call them 'additional' effects.[1] This term, expressing a neutral or open-minded attitude, is helpful; because whatever critics of the medical profession and its pharmaceutical ally may sometimes suggest, many additional effects of drugs are not damaging but actually beneficial and may sometimes even lead to further therapeutic advances. This is true of unexpected, as well as of expected, additional effects. Drug reaction monitoring by drug reaction centres rather than adverse drug reaction monitoring by adverse drug reaction centres might increase the likelihood of observing unexpected desirable effects without losing the power to detect the unwanted ones.

Such additional effects, like any others, are changes observed by the patient or by the physician, in the course of treatment intended to produce effects other than those observed. They may be signs or symptoms, and may take any form to which expression can be given: from euphoria to impotence, from hyperfertility to suicide. Under the appropriate circumstances, any of these reactions may be undesirable or desirable. Clearly, the question of side effects is anything but a side issue. Indeed, it is a possible model for some relationships between society and its medical institutions, and may help to determine what is to be done by those concerned – patient, doctor, pharmaceutical company and regulatory authority – when any additional effect is manifested. What actions are necessary or desirable, and why do some members of the chain of interested parties too frequently fail to make them?

Reactions to additional effects by the patient—

To take the patient first: if he or she experiences an additional effect, he may draw it to the attention of the doctor; some patients may do so more readily if it is pleasant than unpleasant, others the reverse. The patient will do this either for confirmation that the doctor really expected it all the time, and so its occurrences indicates that treatment is successful; or because, on the contrary, the patient requires that it be attended to and removed. More than one physician makes use of expected but unwanted additional effects, such as dry mouth or blurred vision; the patient is told that the effect will probably occur. If it does, the confirmation of the doctor's wisdom increases the likelihood of his or her therapeutic usefulness. These are positive aspects. But patients do not always report an additional effect, perhaps because they are unaware of it, deny it, are excessively anxious about its

significance or fatalistic about the outcome. These are unwanted effects due to the additional effect.

—and by the doctor

The doctor's task is at least as hard. The observer observes what he or she is programmed to observe[2]; as the unexpected effect *is* unexpected, by definition, the chances of its perception are much reduced. Some physicians are trained, or have trained themselves, to look for such events actively. There is also a danger here; as is well known to those living in periods of relative unenlightenment, such as the present, the active pursuit of mythological beasts is liable to call them into existence. But if a genuine effect has been detected and the appropriate measures for the patient's wellbeing have been applied, the doctor's interest may not be at an end and his duty certainly not. A serious reaction so much as suspected as due to the ingestion of a drug must be reported: certainly to the statutory authority (although even in those countries which have one, there is no compulsion to do so, only varying degrees of encouragement) and preferably to the manufacturer as well. On the other hand, a number do neither, preferring to publish. Though some physicians, eg, in Switzerland, seem to prefer to communicate with the manufacturer rather than with their own health authority, others (as, it may be, in Canada) seem to be more suspicious of what the manufacturer will do with the information. The safe rule is surely to communicate with both. In Britain, physicians seem to report impartially and equally to manufacturer and to authority. Whether the report is to one, or both, problems remain: how serious is 'serious'? And how is the physician to be sure that the effect is indeed drug-related? If the drug is relatively new and thus at the beginning of its public history, there will be little to go on except experiences with older drugs of similar structure or clinical actions. Any initial observation can always be dismissed as chance; and subsequent reports are naturally more likely to be dismissed in the same way if the earlier ones were not recorded. Hence reports are vital.

But even a physician sure of a genuine effect may still be reluctant to pass on the information,[3] for a report may produce a written enquiry and perhaps a visit from a field monitor. And although doctors may have been reassured that such a contact is only for the purpose of collecting further information, they may still see it as some kind of criticism, for example, of their prescribing practice, or even threat by a bureaucratic inspector or their own colleagues. Whether there is such a visit or not, the doctor has to fill in yet another form. Nevertheless, the pen must be taken out a second time, if the occasion of its first use led to an important additional effect. Concern about confidentiality is another reason for not reporting side effects.

Manufacturer's duty to collect information relating to its drugs

The duties of the pharmaceutical manufacturer are no less clear. It must do everthing it can to collect information about *all* effects, good and bad, of drugs that it produces or for which it is responsible. These duties are not only to its shareholders and employees but to the whole society of which it is part, including doctors and patients. All these duties are in line with its economic interests; the fullest knowledge about the usefulness and tolerability of the product must be obtained in order to improve it or to use it widely.

Collaboration between doctors and drug companies

But the goals are not necessarily easy to achieve; perhaps only a higher (organizational) authority can systematically collect information from different sources and begin the frustrating task of evaluating it in a useful way. A central authority should have power to secure maximally efficient reporting by the medical profession; the manufacturer, however, will know more about the toxicological and clinical properties of the drug than any central authority. The two should therefore clearly work together. Such collaboration would appear capable of solving some problems; for example, by setting up a controlled trial to determine the exact incidence of undesirable effects before the drug appears on the market. On the other hand, it is a doubtful ethic that permits patients to be given a drug to see how toxic it is rather than how beneficial; and 40 053 patients would also need to receive it to give a 95 per cent chance of detecting an incidence of 1 in 10 000,[4] a frequency generally regarded as important, if the effect is important too. Further, even were trials to determine relatively acute effects possible on such a gigantic scale, they would be irrelevant to the increasingly urgent problem of 'delayed' drug-induced disease, in which the latency between stimulus and response may extend over years; perhaps, as in the case of thalidomide or stilboestrol, affecting the next generation.[5] But too often neither the manufacturer nor the authority is given the full facts. Even when the physician does report, he may not mention important matters that can affect the drug response: the age and sex of the patient; the dose and the duration for which the suspected drug has been taken may be missing and resist attempts to recapture them. Individual reactions to drugs differ for a variety of reasons[6]: genetic, dietary, experiential. There are continual changes in the individual's internal and external milieux. Information is also needed about other drugs which the patient may have been prescribed or have been taking on his own account, an area of which even family physicians are still surprisingly

ignorant. Such a list should include aspirin, purgatives, antihistamines, coffee,[7] alcohol, tobacco and cannabis.[8] Those with at least one drug in their bloodstream at any time are not far from a majority. (A 'street' sample in 1968 of American adults contained 14 per cent who had taken a centrally active drug within the previous 24 hours.[9]) And those taking one drug, prescribed or not, are likely to be taking at least one other.[10] The average number of prescribed drugs taken by hospital patients receiving any drug treatment at all lies between six and 10, according to whether they are hospitalized in Jerusalem or Boston[11]; the incidence of unwanted effects varies from 0.5 to 25 per cent in various studies, depending on definitions and methods.[12]

The fact that the larger the number of drugs taken by a patient, the less likely it is that they will all have been provided by a single manufacturer is another argument for collaboration. As the number of drugs taken increases, the more difficult it is to attribute any drug reaction correctly to a definite and single cause. This is also, on balance, an argument in favour of collaboration. Further, manufacturer and central authority desire to give early warning of serious effects so that practising physicians may take appropriate measures for the benefit of their patients. The manufacturer, in addition, is understandably interested to determine how the tolerability of its own drug compares with that of others. The understandable desire of the authorities, on the other hand, to avoid the charge of passing on commercially useful information to competing firms imposes limits on free exchange with manufacturers.

Drug monitoring surveys

Perhaps for this as well as other reasons, such enquiries are also often founded independently, either on an international or on a local basis[13,14] like the drug monitoring surveys based respectively in Boston and Aberdeen, Scotland. The logical design of such systems was first proposed by Finney.[15] Although the multinational manufacturer is arguably a better citizen of the world than any purely national authority can be, the latter cannot afford to ignore what is happening outside its own borders. But any monitoring unit, however large, can only sample a certain area, country or region. As in any experiment, generality is sacrificed by using a sample as a basis for enquiry, and so the validity of the conclusions is diminished. Further, as the basic activity of such a unit is expensive and time-consuming but rather uninspiring, the discovery and reporting of negative rather than positive effects may be more stimulating. It is not necessarily true that, because such investigations are usually based upon hospital inpatient surveys, negative effects are easier to find; although inpatients are known to be different from outpatients or those who are not patients at all (for otherwise they would not be in hospital), conclusions from such surveys, as with clinical trials, are sometimes stated in terms that are too general.

Yet drug effect surveys of this kind do have one substantial advantage over other forms of reporting and must be properly organized to exploit it. They can at least provide estimates of the frequency of occurrence of effect A, associated with use of drug X. For one must know not only how many times the unwanted effect occurred and can be accurately attributed to the use of the drug, but also how many times in total the suspected drug was administered to the population from which the sample of response was drawn; as well as, ideally, the frequency of the effect in the absence of drug administration. Though the first quantity, the numerator, may be difficult enough to estimate, because the event may be underreported[2] or overreported,[16] the same problems are even greater in relation to the denominator. Well defined hospital populations, or other atypical groups, such as physicians themselves, may provide reliable estimates of both; but these may not be valid for other groups. The undertaking involves much labour, and it might be valuable for such surveys to collect information about the occurrence of true iatrogenetic, ie, doctor-induced, effects,[17] as well as those caused by drugs.

Relative importance of additional effects of drugs

The definitions have so far been considered mainly in terms of frequency, but relative importance must somehow be considered as well. This may be as difficult, at times, as comparing the toxicity of Lombard Street with that of a clockwork orange. Surely, if a drug kills five but cures 15 the decision might depend on whether the five were murderous psychopaths and the 15 Nobel prize winners rather than the other way around: nevertheless, the drug may still be considered too dangerous to leave in the hands of the professionals, even those best qualified to use it. This case is of course pure fantasy, but it describes one kind of dilemma. When is the balance of equity definitely disturbed? Is one death to 100 cures ever acceptable? To 1 000 sometimes? To 1 000 000 always? The answer may well depend upon what is being cured, for example, a headache or a malignancy. Problems of decision remain and determine consequent actions. This kind of account must be drawn up, and in a consistent way, if society is not to risk losing definite benefits in exchange for saving uncertain costs.

Separation of costs and benefits

Little has been written here, deliberately, about the statistical basis of modern clinical experiment-

ation. It has taken about a generation to persuade clinicians and managers alike to admit that such methods are necessary in order to arrive at any conclusion, and it may take at least as long to modify their resulting obsession with the calculus of probabilities by use of the calculus of decisions.[18] Even well designed experiments that permit no conclusions do not allow one the luxury of escaping decisions[9,19]. If patients forego treatment after reading such tracts as *Medical Nemesis*,[20] their decision is consequent upon the conclusions of someone else; emotive rather than scientific conclusions, no doubt stimulating to some, potentially lethal to others – an author's meat, a patient's poison. There is no simple choice between good medicine and bad medicine (or no medicine at all); or between drugs with only bad effects and those with only good effects. All drugs surviving exhaustive testing still have both. The separation of costs and benefits must continue to be the object of intensive research,[21] but they can never become fully independent of each other. It is hard to get clean if you throw away the soap because it dirties the water.

References

[1]Despopoulos, A (1975. Personal communication.

[2]Abercrombie, M J (1960). *The Anatomy of Judgment*. London: Hutchinson.

[3]Inman, W H W (1971). Why report adverse drug reactions? *Adverse Drug Reaction Bulletin*, **27**, 76–79.

[4]Wendel, H A (1969). Adverse drug effects and the controlled clinical trial. *Pharmacologica clinica*, **2**, 58–62.

[5]Editorial (1974). Delayed iatrogenic diseases. *Southern Medical Journal*, **67**, 1271–1274.

[6]Kupfer, D J, and Detre, T P (1971). Once more – on the extraordinary side effects of drugs. *Clinical Pharmacology and Therapeutics*, **12**, 575–582.

[7]Editorial (1975). Anxiety symptoms and coffee drinking. *British Medical Journal*, **1**, 296–297.

[8]Joyce, C R B (1974). In: Blum, R H, Bovet, D, and Moore, J: *Controlling Drugs*, chapter 9, 'Experiments and surveys on drug dependence'. San Francisco: Jossey-Bass.

[9]Parry H (1968). The use of psychotropic drugs by US adults. *US Public Health Report*, **83**, 799–810.

[10]Blum, R H, and associates (1969). *Society and Drugs*, No 1, chapter 11. San Francisco: Jossey-Bass.

[11]Levy, N, Nir, I, Birnbaum, D, Superstine, E, and Eliakim, M (1973). Adverse reactions to drugs in hospitalized patients. *Israel Journal of Medical Science*, **9**, 617–626.

[12]Wang, R I, and Terry, L C (1971). Adverse drug reactions in a Veterans Administration Hospital. *Journal of Clinical Pharmacology*, **11**, 14–18.

[13]International drug monitoring: The role of the hospital (1969). *WHO Technical Report Series*, 425.

[14]International drug monitoring: The role of national centres (1972). *WHO Technical Report Series* 498.

[15]Finney, D J (1965). The design and logic of a monitor of drug use. *Journal of Chronic Disease*, **18**, 77–98.

[16]Hart, F D (1973). The importance of non-disease. *Practitioner*, **211**, 193–196.

[17]Balint, M, Hunt, J, Joyce, C R B, Marinker, M, and Woodcock, J J (1970). *Treatment or diagnosis: A study of repeat prescriptions in general practice*. London: Tavistock.

[18]Stewart, T R, Joyce, C R B, and Lindell, M (1975). In: Hammond, K R, and Joyce, C R B (ed): *Social judgment and psycho-active drugs*. New York: Wiley Interscience.

[19]Meier, P (1975). Statistics and medical experimentation. *Biometrics*, **31**, 511–529.

[20]Illich, I (1975). *Medical Nemesis: The expropriation of health*. London: Calder and Boyars.

[21]Mach, E P, and Venulet, J (1975). Counting the cost of adverse drug reactions. *Adverse Drug Reaction Bulletin*, **54**, 184–187.

Commentary

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Why don't manufacturers provide better drug information?

Joyce touches only briefly on the central issue which should determine the use of a drug, namely, the balance which must be struck between the likely benefit and the possible harm that may result from its use. As doctors we need to weigh this balance for drugs that might be used in a particular situation, and we must do this afresh whenever a new piece of relevant information becomes available. The persistent and skilful advocacy aimed at us by the pharmaceutical industry makes it more difficult to reach sound judgments about drugs, so all we can do is try.

Whose responsibility is it to provide for prescribers and patients the information which may allow such a judgment to be made? On the face of it it is the duty of the pharmaceutical manufacturers, or in the case of an unbranded formulary preparation, the agency producing the formulary. Information about drugs is customarily presented under several headings. The meaning of 'indications and contra-indications' may seem very clear but on analysis is less so. Since manufacturers wish to maximize their sales they usually try to suggest as many indications as they can persuade themselves are reasonable, but only a proportion of these uses are medically appropriate. Where there is more acceptable and certain therapy, to use a preparation which is doubtfully effective might be harmful. Examples abound but two from the makers of the new penicillins may be used to illustrate this.

The makers of cloxacillin and flucloxacillin state that these drugs are 'indicated for the treatment of

infections due to Gram-positive organisms, including infections caused by penicillin-resistant staphylococci' (Association of the British Pharmaceutical Industry Data Sheet, 1976, pp 77, 79) and list among a variety of other conditions otitis media and pneumonia. From a medical point of view, however, these drugs should be used to treat infections due to staphylococci that are, or are likely to be, penicillin-resistant. Infections caused by other Gram-positive organisms are more appropriately treated with benzyl penicillin or penicillin V because these are more active against such organisms than cloxacillin or flucloxacillin. Likewise it is never openly stated in the manufacturer's literature on ampicillin that this antibiotic is ineffective against penicillin-resistant staphylococci (Association of the British Pharmaceutical Industry Data Sheet, 1976, p 80).

A cluster of problems may surround a drug which makes its use equivocal. Clioquinol is traditionally taken to prevent and treat traveller's diarrhoea, but no good evidence exists that it is effective (Dunne, Flood and Herxheimer, 1976). The patient using this drug might neglect other prophylactic or therapeutic measures against diarrhoea that are more likely to help. In this instance, however, there is also a small risk of positive harm from the preparation, since for example a traveller using it as prophylaxis might increase his chance of becoming a salmonella carrier. Even a drug with a serious adverse effect may not have this clearly stated in the data which are supplied. Chloramphenicol was suggested in many countries for use in a wide range of infections, including viral, intestinal, respiratory, gynaecological and venereal infections. The use of the drug in these conditions is appropriate only very rarely, where infections are resistant or much less sensitive to other antibiotics, and a drug which does not carry the risk of irreversibly damaging the bone marrow is to be preferred. Only in a few countries do the manufacturer's indications make this clear (Dunne, Herxheimer, Newman and Ridley, 1973). A survey of 576 cases of blood dyscrasias attributed to chloramphenicol showed that only 5 per cent of patients were prescribed the drug for the treatment of typhoid or paratyphoid infection; in most of the others an alternative drug would have been a better choice (Polak *et al*, 1972).

Another heading that is almost universally used in drug information is 'warnings', 'side effects', and/or 'precautions'. Here the manufacturer tries to summarize untoward events that may occur during the use of the drug, how their occurrence may be minimized, and how they should be managed when they occur. This poses a problem for the manufacturer and the user. If the list is exhaustive it will be much too long to be assimilated and used by the prescriber; if it is not complete it invites the charge that it is not honest. A compromise must obviously be made, and this may tempt manufacturers to underemphasize the risk of unwanted effects, for it is not in their interest to put prescribers off using the drug. Warnings may be played down by using a phrase such as 'side effects . . . are rare . . .', as in the data sheet for ampicillin; or a justly phrased warning may be buried in a mass of other information so that it is hard to find, and when found seems less important than it is. An example is the warning about the effect of Achromycin V (buffered tetracycline) in patients with renal failure (Association of the British Pharmaceutical Industry Data Sheet, 1976, p 410).

Chloramphenicol also illustrates the important point that benefit or lack of harm to the individual patient is not the only question to be considered if the balance is to be properly weighed. Recently chloramphenicol-resistant typhoid has emerged, to the alarm of all those dealing with this disease. This is almost certainly due at least in part to the unwise overprescribing of this antibiotic. Antistaphylococcal and antituberculous drugs similarly need careful use, and wrong prescribing, whether encouraged or not by promotion, may cause drug-resistant organisms to emerge to threaten a community. Immunization is an area where hazard to the individual has sometimes been outweighed by benefit to the community, as in the routine use until recently in Britain of smallpox vaccination. The current argument for continuing to use whooping-cough vaccine seems to contain something of this emphasis. Decisions become more difficult, but nonetheless important, when powerful drugs easily pass into the hands of those who may abuse them. When these drugs are of uncertain value to the patient, such as antidepressives used to combat situational stress, or have been superseded by safer medicines, eg, barbiturates as hypnotics or sedatives, their use must be re-evaluated.

To whom should this task be entrusted? Since it is so difficult for manufacturers to provide information about their products which is balanced from a medical point of view, this clearly needs to be provided by a professionally acceptable body that has no commercial interests in the preparation. It should ideally be independent from government, though it might well be officially supported. In theory the Committee on Safety of Medicines and its secretariat could do the job, but it would need to be greatly enlarged.

The need for a national body which can assess medicines is particularly pressing when existing information and practice must be changed in the light of new observations, as happened with the use of fluorinated corticosteroid creams on the face. At an early stage it may not be clear what type of warning should be given, and needless alarm may harm more people than a necessary warning would protect. This happened when the dangers of

thromboembolism caused by oral contraceptives with a high oestrogen component were publicized in 1969. A mature approach and speedy and decisive action are needed both from the manufacturer and the regulatory authority. In the United Kingdom, the recent withdrawal of Volidan and the warnings about the hazards of practolol were handled well and suggest that a reasonable balance is now being struck here.

New drugs are now surrounded by such stringent controls that some people feel we are in danger of losing useful preparations. However, although the laboratory work which must be done before a drug is used clinically is closely scrutinized and is usually satisfactory, most early clinical trials of drugs are too limited to give clear answers to the questions that most concern clinicians. It would be better for the community if the manufacturer had to demonstrate a need for his new drug before being allowed to market it. At present, in many areas, new products such as beta-blockers and anti-inflammatory analgesics, are being introduced for no medically convincing reason. This offers us plentiful new risks of unwanted effects without providing clear-cut new benefits. The problems will not go away: manufacturers, doctors and regulatory authorities must face them.

References

Association of the British Pharmaceutical Industry (1976) Data Sheet Compendium.

Dunne, M, Flood, M, and Herxheimer, A (1976). Clioquinol: availability and instructions for use. *Journal of Antimicrobial Chemotherapy* **2**, 21–29.

Dunne, M, Herxheimer, A, Newman, M, and Ridley, H (1973). Indications and warnings about chloramphenicol, *Lancet* **2**, 781–3.

Polak, B V P, Wesseling, H, Schut, D, Herxheimer A, and Meyler L, (1972). Blood dyscrasias attributed to chloramphenicol, *Acta Medica scandinavica*, **192**, 409–414.